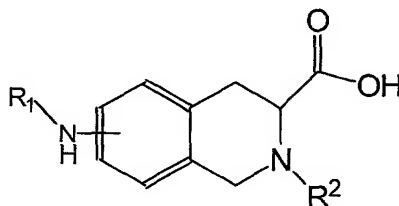


What is claimed is:

1. A method of preparing an  $R^1$ ,  $R^2$ -substituted-amino-substituted-tetrahydroisoquinoline-carboxylic acid having the structure:



wherein  $R^1$  is alkyl, aryl, heterocyclic moiety, amide, sulfonamide, urea, thiourea, or alcohol and  $R^2$  is alkyl, aryl, heterocyclic moiety, amide, sulfonamide, urea, thiourea, alcohol, or hydrogen, the method comprising the steps of: (a) providing an orthogonally protected amino-substituted-tetrahydroisoquinoline-carboxylic acid wherein the orthogonally protected amino-substituted-tetrahydroisoquinoline-carboxylic acid is attached to a solid support and in the form of a carboxylate; (b) attaching an  $R^1$  group to the orthogonally protected amino-substituted-tetrahydroisoquinoline-carboxylate; (c) deprotecting the orthogonally protected  $R^1$ -substituted amino-substituted-tetrahydroisoquinoline-carboxylate; (d) attaching an  $R^2$  group to the ring nitrogen of the deprotected  $R^1$ -substituted-amino-substituted-tetrahydroisoquinoline-carboxylate to form an intermediate attached to the solid support; and (e) cleaving the intermediate from the solid support to form an  $R^1$ ,  $R^2$ -substituted-amino-substituted-tetrahydroisoquinoline-carboxylic acid.

2. A method according to claim 1, wherein the step of cleaving the intermediate from the solid support comprises treating the intermediate with HBr.

3. A method according to claim 2, wherein the step of cleaving the intermediate from the solid support comprises treating the intermediate with a composition comprising from about 1% to about 2%, by weight, HBr and trifluoroacetic acid.

4. The method according to claim 1, wherein step a comprises: (i) providing a nitro-substituted-tetrahydroisoquinoline-carboxylic acid with a protecting group to form an orthogonally protected nitro-substituted-tetrahydroisoquinoline-carboxylic acid; (ii) attaching the orthogonally protected nitro-substituted-tetrahydroisoquinoline-carboxylic acid to the solid support to form the carboxylate; and (iii) reducing the nitro group to form the orthogonally protected amino-substituted-tetrahydroisoquinoline-carboxylate.

5. A method according to claim 1, wherein the protecting group is selected from the group consisting of t-butyloxycarbonyl, 9-fluorenylmethoxycarbonyl, benzyloxycarbonyl, allyloxycarbonyl, (trimethylsilyl)ethoxycarbonyl and mixtures thereof.

6. A method according to claim 1, wherein the solid support is a polystyrene resin.

7. A method according to claim 1, wherein step b comprises reacting the orthogonally protected amino-substituted-tetrahydroisoquinoline-carboxylate with benzoyl chloride in the presence of N,N-diisopropylethylamine.

8. A method according to claim 1, wherein step d comprises reacting the R<sup>1</sup>-substituted-amino-substituted-tetrahydroisoquinoline-carboxylate with benzaldehyde in a borane/pyridine complex.

9. A method according to claim 1, wherein the step of attaching the R<sup>1</sup> group comprises a step selected from the group consisting of: (i) reacting the orthogonally protected amino-substituted-tetrahydroisoquinoline-carboxylate with an acyl chloride in the presence of N,N-diisopropylethylamine and dichloroethane; (ii) activating a carboxylic acid in solution using (benzotriazol-1-yloxy)-tris(pyrrolidino)phosphonium hexafluorophosphate in dimethylformamide, and adding the solution to the orthogonally protected amino-substituted-tetrahydroisoquinoline-carboxylate; (iii) activating a N-protected amino acid in solution using (benzotriazol-1-yloxy)-tris(pyrrolidino)phosphonium

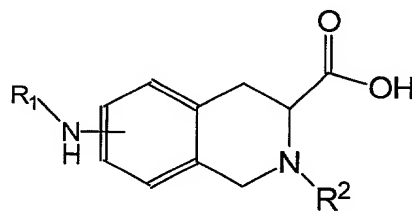
hexafluorophosphate in dimethylformamide, and adding the solution to the orthogonally protected amino-substituted-tetrahydroisoquinoline-carboxylate; (iv) reacting the orthogonally protected amino-substituted-tetrahydroisoquinoline-carboxylate with a sulfonyl chloride in the presence of 4-dimethylaminopyridine and pyridine; (v) reacting the orthogonally protected amino-substituted-tetrahydroisoquinoline-carboxylate with an isocyanate in the presence of NaH in dimethylformamide; (vi) reacting the orthogonally protected amino-substituted-tetrahydroisoquinoline-carboxylate with an isothiocyanate in the presence of NaH in dimethylformamide; (vii) reacting the orthogonally protected amino-substituted-tetrahydroisoquinoline-carboxylate with an epoxide in the presence of an alcohol solvent; (viii) reacting the orthogonally protected amino-substituted-tetrahydroisoquinoline-carboxylate with an alkyl halide in the presence of Bu<sub>4</sub>NHSO<sub>4</sub> and Na<sub>2</sub>CO<sub>3</sub>; and (ix) reacting the orthogonally protected amino-substituted-tetrahydroisoquinoline-carboxylate with an aldehyde in the presence of a borane/pyridine complex.

10. A method according to claim 1, wherein the step of attaching the R<sup>2</sup> group comprises a step selected from the group consisting of: (i) reacting the R<sup>1</sup>-substituted-amino-substituted-tetrahydroisoquinoline-carboxylate with an acyl chloride in the presence of N,N-diisopropylethylamine and dichloroethane; (ii) activating a carboxylic acid in solution using (benzotriazol-1-yloxy)-tris(pyrrolidino)phosphonium hexafluorophosphate in dimethylformamide, and adding the solution to the R<sup>1</sup>-substituted-amino-substituted-tetrahydroisoquinoline-carboxylate; (iii) activating a N-protected amino acid in solution using (benzotriazol-1-yloxy)-tris(pyrrolidino)phosphonium hexafluorophosphate in dimethylformamide, and adding the solution to the R<sup>1</sup>-substituted-amino-substituted-tetrahydroisoquinoline-carboxylate; (iv) reacting the R<sup>1</sup>-substituted-amino-substituted-tetrahydroisoquinoline-carboxylate with a sulfonyl chloride in the presence of 4-dimethylaminopyridine and pyridine; (v) reacting the R<sup>1</sup>-substituted-amino-substituted-tetrahydroisoquinoline-carboxylate with an isocyanate in the presence of NaH in dimethylformamide; (vi) reacting the R<sup>1</sup>-substituted-amino-substituted-tetrahydroisoquinolin-carboxylate with an isothiocyanate in the presence

of NaH in dimethylformamide; (vii) reacting the  $R^1$ -substituted-amino-substituted-tetrahydroisoquinoline-carboxylate with an epoxide in the presence of an alcohol solvent; (viii) reacting the  $R^1$ -substituted-amino-substituted-tetrahydroisoquinoline-carboxylate with an alkyl halide in the presence of  $Bu_4NHSO_4$  and  $Na_2CO_3$ ; and (ix) reacting the  $R^1$ -substituted-amino-substituted-tetrahydroisoquinoline-carboxylate with an aldehyde in the presence of a borane/pyridine complex.

11. A method according to claim 1, wherein the amino-substituted-tetrahydroisoquinoline-carboxylic acid is 7-amino-tetrahydroisoquinoline-carboxylic acid.

12. A method of preparing a combinatorial library of amino-substituted-tetrahydroisoquinoline-carboxylic acids having the structure:



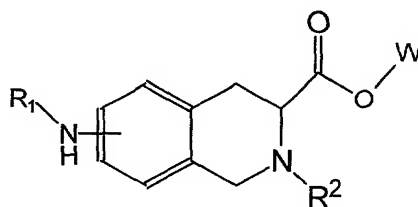
wherein  $R^1$  is alkyl, aryl, heterocyclic moiety, amide, sulfonamide, urea, thiourea, or alcohol, and  $R^2$  is alkyl, aryl, heterocyclic moiety, amide, sulfonamide, urea, thiourea, alcohol or hydrogen, the method comprising the steps of: (a) providing an orthogonally protected amino-substituted-tetrahydroisoquinoline-carboxylic acid wherein the orthogonally protected amino-substituted-tetrahydroisoquinoline-carboxylic acid is attached to a solid support and in the form of a carboxylate; (b) attaching a first  $R^1$  group to a first portion of the orthogonally protected amino-substituted-tetrahydroisoquinoline-carboxylate and attaching a second  $R^1$  group to a second portion of the orthogonally protected amino-substituted-tetrahydroisoquinoline-carboxylate; (c) deprotecting the first and second portions of the orthogonally protected amino-substituted-tetrahydroisoquinoline-carboxylates to form first and second deprotected amino-substituted-tetrahydroisoquinoline-carboxylates; (d) attaching a first  $R^2$  group to the ring nitrogen of the first

deprotected amino-substituted-tetrahydroisoquinoline-carboxylate to form a first intermediate and attaching a second  $R^2$  group to the ring nitrogen of the second deprotected amino-substituted-tetrahydroisoquinoline-carboxylate to form a second intermediate; and (e) cleaving the first and second intermediates from the solid support to form a first and second  $R^1$ ,  $R^2$ -substituted-amino-substituted-tetrahydroisoquinoline-carboxylic acids; wherein at least one of the first  $R^1$  group and the first  $R^2$  group is different from the second  $R^1$  group and the second  $R^2$  group, respectively.

13. A method according to claim 12, wherein the step of cleaving the first and second intermediates from the solid support comprises treating the intermediates with HBr.

14. A method according to claim 12, wherein the amino-substituted-tetrahydroisoquinoline-carboxylic acid is 7-amino-tetrahydroisoquinoline carboxylic acid.

15. A method of preparing an amino-substituted-tetrahydroisoquinoline-carboxylic acid comprising the steps of: (a) providing a support-bound amino-substituted-tetrahydroisoquinoline compound having the structure:



wherein  $R^1$  is alkyl, aryl, heterocyclic moiety, amide, sulfonamide, urea, thiourea, or alcohol, and  $R^2$  is alkyl, aryl, heterocyclic moiety, amide, sulfonamide, urea, thiourea, hydrogen, or alcohol, and W represents a support, and (b) cleaving the support-bound amino-substituted-tetrahydroisoquinoline compound to form an amino-substituted-tetrahydroisoquinoline-carboxylic acid.

16. A method according to claim 15, wherein the step of cleaving the intermediate from the solid support comprises treating the intermediate with HBr.

17. A method according to claim 15, wherein the solid support is a polystyrene resin.

18. A method according to claim 15, wherein the amino-substituted-tetrahydroisoquine-carboxylic acid is 7-amino-tetrahydroisoquinoline carboxylic acid.

19. A method of preparing an amino-substituted-tetrahydroisoquinoline-carboxylic acid comprising the steps of: (a) providing a support-bound amino-substituted-tetrahydroisoquinoline-carboxylic acid in the form of a carboxylate, wherein the ring nitrogen of the support-bound amino-substituted-tetrahydroisoquinoline has a protecting group; (b) attaching a first moiety to the 7-amino group of the support-bound amino-substituted-tetrahydroisoquinoline-carboxylate having a protecting group; (c) removing the protecting group from the ring nitrogen of the support-bound amino-substituted-tetrahydroisoquinoline-carboxylate; (d) attaching a second moiety to the ring nitrogen of the support-bound amino-substituted-tetrahydroisoquinoline-carboxylate to form a support-bound intermediate; and (e) cleaving the support-bound intermediate from the solid support to form an amino-substituted-tetrahydroisoquinoline-carboxylic acid.

20. A method according to claim 19, wherein the step of cleaving the support-bound intermediate from the solid support comprises treating the intermediate with a composition comprising HBr and trifluoroacetic acid.

21. A method according to claim 19, wherein the solid support is a resin.

22. A method according to claim 19, wherein the amino-substituted-tetrahydroisoquinoline-carboxylic acid is 7-amino-tetrahydroisoquinoline-carboxylic acid.